Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Teva

MHRA Inspection Number: Insp GPvP 289/4151423-0003

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ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CAP	Centrally Authorised Product
CAPA	Corrective and Preventative Action
CCDS	Company Core Data Sheet
CHMP	Committee for Medicinal Products for Human Use
CRO	Contract Research Organisation
CSR	Clinical Study Report
DCP	Decentralised Procedure
DHPC	Direct Healthcare Professional Communication
DSUR	Development Safety Update Report
EMA	European Medicines Agency
EU	European Union
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
GVP	Good Vigilance Practice
HCP	Healthcare Professional
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
KPI	Key Performance Indicator
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRP	Mutual Recognition Procedure
NAP	Nationally Authorised Product
NCA	National Competent Authority
NIS	Non-Interventional Study
PAES	Post-Authorisation Efficacy Study
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit Risk Evaluation Report

PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
PVA	Pharmacovigilance Agreements
QA	Quality Assurance
QMS	Quality Management System
QPPV	Qualified Person responsible for Pharmacovigilance
RMM	Risk Minimisation Measures
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDEA	Safety Data Exchange Agreement
SmPC	EU Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
UK	United Kingdom
XEVMPD	eXtended Eudravigilance Medicinal Product Dictionary

SECTION A: INSPECTION REPORT SUMMARY

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Inspection type:	Statutory National Inspection
System(s) inspected:	Teva Pharmaceutical Industries [redacted]
Site(s) of inspection:	Field House, Station Approach, Harlow CM20 2FB
Main site contact:	[redacted]
Date(s) of inspection:	22nd July 2019 – Office based inspection 23rd – 26th July 2019 – on site inspection
Lead Inspector:	[redacted]
Accompanying Inspector(s):	
Previous inspection date(s):	Teva UK Ltd inspected: 19 – 21 September 2012 14 – 17 March 2011 17 – 20 August 2009
Purpose of inspection:	Inspection of pharmacovigilance systems to review compliance with UK and EU requirements.
Products selected to provide system examples:	No specific products were selected for review.
Name and location of EU QPPV:	[redacted] PhD Teva GmbH, Graf Arco Strasse 3, 89079 Ulm, Germany [redacted]
Global PV database (in use at the time of the inspection):	ARISg (commercially available)
Key service provider(s):	Accenture completing performing case processing activities. Adis-Springer performing weekly literature searches.
Inspection finding summary:	5 Major findings 3 Minor findings
Date of first issue of report to MAH:	31 October 2019
Deadline for submission of responses by MAH:	16 December 2019 (1) 25 February 2020 (2)
Date(s) of receipt of responses from MAH:	16 December 2019 (1) 25 February 2020 (2)
Date of final version of report:	12 March 2020
Report author:	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Teva was selected for routine inspection as part of the MHRA's statutory, national pharmacovigilance inspection programme. The purpose of the inspection was to review compliance with currently applicable EU and UK pharmacovigilance regulations and guidelines. In particular, reference was made to Regulation 726/2004/EC as amended, Directive 2001/83/EC as amended, Commission Implementing Regulation (EU) No 520/2012 and the adopted good pharmacovigilance practices (GVP) Modules.

A list of reference texts is provided at Appendix I.

Teva is a global pharmaceutical company, headquartered in Petah Tikva, Israel. Global pharmacovigilance is located in Netanya, Israel; and is comprised of six functions: Medicial Scientific Unit, Global PhV operations, Global PhV Data Management, Global PhV Compliance, Teva Periodic Report & Risk Management Centre and the EU QPPV. There are two regional hubs, International markets and North America and Europe, which report into Global pharmacovigilance. The European regional hub is comprised of six clusters, of which the UK/IE/NL cluster is one. The clusters report into the Head of EU Pharmacovigilance, which is the EUQPPV.
Teva held over 1,000 marketing authorisations in the UK at the time of the inspection. The PSMF was located in Croatia, and the supervisory authority was HALMED.

This inspection was conducted after the supervisory authority inspection had been conducted in November and December 2018. The inspection report had not been finalised, but remedial activities were in progress at the time of this inspection.

B.2 Scope of the inspection

The inspection included a review of the local (UK) and global pharmacovigilance systems and was performed at Teva's offices in Harlow, Essex. Personnel attended the site and were available via teleconference where necessary in order to participate in the inspection.

The inspection was performed using interviews and document review (including outputs from the global safety database and listings of medical information enquiries and product complaints). The systems reviewed during the inspection are highlighted in the Pharmacovigilance Inspection Plan (attached as Appendix II).

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B.3 Documents submitted prior to the inspection

The company submitted a PSMF (last [redacted] to assist with inspection planning and preparation. Specific additional documents were also requested by the inspection team and provided by the company prior to the inspection.

B.4 Conduct of the inspection

In general, the inspection was performed in accordance with the Inspection Plan.

The inspection included a scheduled office-based inspection day, which was held on 22nd July 2019, the purpose of which was to review procedural documentation prior to the on-site inspection days.

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A closing meeting was held to review the inspection findings at the Teva offices in Harlow on 26th July 2019. A further teleconference was held with Teva to discuss CAPA for MA.1 on the [redacted]

A list of the personnel who attended the closing meeting is contained in the Closing Meeting Attendance Record, which will be archived together with the inspection notes, a list of the documents requested during the inspection and the inspection report.

SECTION C: INSPECTION FINDINGS

C.1 Summary of significant changes to the pharmacovigilance system prior to the inspection

The following notable changes to the pharmacovigilance system had occurred prior to the inspection.

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- The EUQPPV had changes from [redacted] in April 2018
- Teva had acquired the [redacted] consisting of legacy Actavis, legacy Warner Chilcott, legacy Auden Mackenzie and legacy [redacted] portfolios in 2016. This acquisition which was subject to a merger review by the EC regarding competition. The outcome of the review was to divest the UK/IE Actavis business to [redacted]
- Following the supervisory authority inspection in November and December 2018, Teva had begun to implement CAPA for the reported findings, however the inspection report had not been finalised at the time of this MHRA inspection.

C.2 Definitions of inspection finding gradings

Critical (CR): a deficiency in pharmacovigilance systems, practices or processes that adversely affects the rights, safety or well-being of patients or that poses a potential risk to public health or that represents a serious violation of applicable legislation and guidelines.

Major (MA): a deficiency in pharmacovigilance systems, practices or processes that could potentially adversely affect the rights, safety or well-being of patients or that could potentially pose a risk to public health or that represents a violation of applicable legislation and guidelines.

Minor (MI): a deficiency in pharmacovigilance systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients.

Comment: the observations provide suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

The factual matter contained in the Inspection Report relates only to those things that the inspection team saw and heard during the inspection process. The inspection report is not to be taken as implying a satisfactory state of affairs in documentation, premises, equipment, personnel or procedures not examined during the inspection.

Findings from any inspection which are graded as critical or major will be shared with the EMA, other EU competent authorities and the European Commission.

C.3 Guidance for responding to inspection findings

Responses to inspection findings should be clear, concise and include proposed actions to address both the identified deficiency and the root cause of the deficiency. Consideration should also be given to identifying and preventing other potential similar deficiencies within the pharmacovigilance system.

Responses should be entered directly into the table(s) in section C.4. The following text is intended as guidance when considering the information that should be entered into each of the fields within the table(s). 'Not applicable' should be entered into the relevant field if the requested information is not appropriate for the finding in question.

Root Cause Analysis Identify the root cause(s) which, if adequately addressed, will prevent recurrence of the deficiency. There may be more than one root cause for any given deficiency.
Further Assessment Assess the extent to which the deficiency exists within the pharmacovigilance system and what impact it may have for all products. Where applicable, describe what further assessment has been performed or may be required to fully evaluate the impact of the deficiency e.g. retrospective analysis of data may be required to fully assess the impact.
Corrective Action(s) Detail the action(s) taken / proposed to correct the identified deficiency.
Preventative Action(s) Detail the action(s) taken / proposed to eliminate the root cause of the deficiency, in order to prevent recurrence. Action(s) to identify and prevent other potential similar deficiencies should also be considered.
Deliverable(s) Detail the specific outputs from the proposed / completed corrective and preventative action(s). For example, updated procedure/work instruction, record of re-training, IT solution.
Due Date(s) Specify the actual / proposed date(s) for completion of each action. Indicate when an action is completed.

Further information relating to inspection responses can be found under 'Inspection outcomes' at: https://www.gov.uk/guidance/good-pharmacovigilance-practice-gpvp

C.4 Inspection findings

C.4.1 Critical findings

No critical findings were identified from the review of pharmacovigilance processes, procedures and documents performed during this inspection.

C.4.2 Major findings

MA.1 Pharmacovigilance Data Management

Requirements:

Commission Implementation Regulation 520/2012 Article 12

GVP Module I – Pharmacovigilance Systems and their Quality Systems

I.C.1.4. *"Documents transferred in situations where the business of the marketing authorisation holder is taken over by another organisation should be complete."*

GVP Module VI - Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)

VI.B.4. *"When transfer of pharmacovigilance data occurs within an organisation or between organisations having set up contractual agreements, the mechanism should be such that there is confidence that all notifications are received; in that, a confirmation and/or reconciliation process should be undertaken."*

VI.B.5. *"…marketing authorisation holders should have a quality management system in place to ensure compliance with the necessary quality standards at every stage of case documentation, such as data collection, data transfer, data management, data coding, case validation, case evaluation, case follow-up, ICSR submission and case archiving (see VI.C.6.2.4. and GVP Module I for EU guidance on data quality of ICSRs)."*

Finding MA.1 a)

Following the acquisition of the Allergan generics portfolio Teva did not hold, or have access to, a significant proportion of source documentation for the cases which had been transferred.

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Four separate data migrations were carried out to transfer safety data from the different legacy companies which Teva had acquired (see table 1).

[redacted]

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[redacted]

Table 1. Teva acquisitions of Allergan products

The cases which had been migrated spanned from 1956 to 2017, further details are included in appendix 1.

Teva stated verbally during the inspection that it was presumed all source data for ex-Forest, Warner Chilcott and Actavis cases had been included as part of the transfer of pharmacovigilance information, but confirmed that missing source documents were identified for Auden Mackenzie cases during a comparison exercise performed in October 2016.

Despite the first indication of missing source documentation being identified in 2016, Teva stated that at the time of the inspection no exercise had yet been undertaken to determine how many migrated cases were missing associated source documentation. It is acknowledged that Teva did attempt, on several occasions, to liaise with the previous MAH to recover the source data.

An evaluation was carried out post-inspection and the information provided is presented in Table 2.

	Number of cases received	Number of cases with Source Documents received	% of cases with Source Documents received	% of cases with no Source Documents received	Number of cases with no Source Documents available
[redacted]					

Table 2. Estimation of numbers of cases without source documentation.

Teva estimate that of [redacted] cases migrated from Allergan, [redacted] did not have source documentation. Approximately [redacted] of cases with missing source documents were spontaneously reported post-marketing cases such that it would be more difficult to reproduce source documents than it would be for literature or regulatory authority cases. Of these, [redacted] were serious, and [redacted] were non-serious.

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Furthermore, [redacted] of these cases were identified as clinical trial cases [redacted] of total) were serious clinical trial cases and [redacted] of total) were non-serious clinical trial cases.

This has been graded as major due to the potential risk to patient safety and is considered a significant breach of legislation. If an important new safety issue lead to the requirement to re-evaluate existing cases for products Teva would be unable to verify the accuracy of the information within their global safety database, or data provided to authorities in response to safety concerns. The lack of source documentation also impedes the ability of the MHRA to verify the coding and assessment of cases which are present in pharmacovigilance databases.

Teva should also note the following in relation to this finding:

It is expected that the CAPA for this finding would include reference to due diligence processes prior to and during acquisition of the licences which are associated with missing source documentation and include details of the due diligence processes in place and whether appropriate due diligence activities were performed. This should be presented alongside the corrective actions which Teva propose to locate the missing source documentation, including any / all mitigations Teva can implement in the absence of source documentation.

The proposed CAPA in response to "*including any / all mitigations Teva can implement in the absence of source documentation*" was discussed with Teva during a teleconference on the [redacted] Following that discussion, CAPA was presented and is outlined in Appendix III.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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Deliverable(s)	Due Date(s)
[redacted]	
Preventative Action(s)	
[redacted]	
Deliverable(s)	**Due Date(s)**
[redacted]	

Finding MA.1 b)

There were errors identified in cases which had been migrated into the Teva global safety database

a) The case seriousness and received dates recorded in cases manually migrated from Merck were not accurate.

i) Cases were identified where the initial received date of the case was incorrectly populated with the date of the migration, as opposed to the initial received date for the case. For example:

- [redacted] (0), where the initial and latest received date was recorded as **12-Jan-2018** in the global safety database, however the case narrative stated the case was received as an Anonymous Single Patient Print from the Medicines Control Agency* (MCA), via Merck Lipha Pharmaceuticals, on **25-Mar-1996.** This case concerned 'subacute hepatocellular necrosis', 'jaundice', 'rash', 'ascites' and 'odema' with [redacted]

The migration from Merck involved a transfer of 'standard E2B XMLs' for [redacted] cases and was following the acquisition of [redacted] by Teva. A review of the line listing from Teva's global safety safety database outlined [redacted] cases that contained [redacted] as a suspect drug and had a latest received date of 12 January 2018, suggesting the majority of the migrated cases had been affected.

ii) Additionally, seven cases from this migration were identified to contain errors in relation to the case seriousness:

- One case [redacted] of hepatic necrosis was identified as serious in

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the source XML which was processed as non-serious in ARISg in error.

- Six cases [redacted] reporting abortion, [redacted] reporting foetal death, [redacted] reporting myocardial infarction, sepsis and pulmonary embolism, [redacted] reporting lung infiltration and respiratory failure, [redacted] reporting circulatory collapse and 2018-[redacted] reporting cardiac arrest) did not include seriousness assessments in the source XML files and were incorrectly processed as non-serious.

b) There were cases identified which were missing case level seriousness.

i) Cases from the legacy [redacted] migration had no case level seriousness populated in the global safety database. Case ID's included [redacted]

Teva informed the inspection team that these cases had undergone manual review following the migration due to discrepancies identified with the adverse events. During the correction of these cases the case level seriousness had not been populated.

*N.B. The MCA merged with the Medical Devices Agency (MDA) in 2003 to form the MHRA.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

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[redacted]

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Corrective Action(s)
[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Preventative Action(s)
[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

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[redacted]

Finding MA.1 c)

There was one example identified where an end-of-study reconciliation had not taken place to ensure all adverse drug reactions had been collected by Teva from the CRO.

Study [redacted] *SPRINT- A Phase IV Real-World Multi-Country Observational Study on Patients' Disease Control and Self-Reported Outcomes During Fixed Dose Combination Inhaler Treatment for Persistent Asthma and COPD*, was a non-interventional, prospective study conducted voluntarily with study sites in Denmark, Norway, Sweden, Italy, the Netherlands, Ireland, Croatia Spain, Portugal and the United Kingdom. The study was conducted from June 2015 to April 2017. A total of 1661 patients participated in the study, of which [redacted] were enrolled at UK study sites. Teva had outsourced the management of this study to a CRO, Experior S.L.

The safety management plan [redacted] dated 23 Feb 2016) stated in section 11.2, titled "Event Reconciliation":

> *"[…] at the end of the study, Experior will initiate reconciliation activities by requesting line listings from Global Pharmacovigilance via Safety.AE@teva.co.il, for all reported events, also asking for confirmation regarding the MedDRA version in which events were coded for the listing. […]*
>
> *Experior has responsibility for the reconciliation of the clinical and safety databases and will maintain communication with Global Pharmacovigilance to complete this task."*

There was no evidence which demonstrated that an end-of-study reconciliation was conducted between Teva and Experior S.L., at the end of the study in April 2017.

[redacted]

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Preventative Action(s)

[redacted]

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Deliverable(s)	Due Date(s)
[redacted]	

MA.2 Signal Management

Requirements:

GVP Module XI - Signal Management (Rev 1)

IX.C.1.1. "*...signals should be reported to the competent authorities in the EU as appropriate, taking into account the general obligations of the marketing authorisation holder to keep their product information up-to-date throughout the product's lifecycle by variation applications and to present comprehensive signal information in PSURs." [emphasis added]*

Module IX Addendum I – Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions

IX. Add I.2.1. "*Disproportionality statistics take the form of a ratio of the proportion of spontaneous ICSRs of a specific adverse event with a specific medicinal product to the proportion that would be expected if no association existed between the product and the event.*" [Emphasis added]

Product- or Population-Specific Considerations II: Biological medicinal products

P.II.B.4. "*Processes should be particularly sensitive to detect any acute and serious new risks that may emerge following a change in the manufacturing process or quality of a biological and important differences between batches of the same product (this is particularly important following a significant change to the manufacturing process given that the product name usually does not change).*"

"*Any signal should be evaluated in the context of batch-specific exposure data, including numbers/codes of delivered or sold batches, their size and the regions or countries where the respective batches have been delivered.*"

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Finding MA.2 a)

There were signals which had not progressed through the signal management process in a timely manner.

Signal management [redacted] "Signal Management" [redacted], effective 06 Apr 2018) [redacted] outlined the process for assigning a priority for validated signals, from category 1 "Low-risk priority" to category 4 "Very high-risk".

The categories determined the length of time taken from the validation date to the signal evaluation report to be written and presented in a signal evaluation meeting, or product safety group meeting for actions to be considered. Category 1 had a timeframe of 12 months, and Category 2 had a timeframe of six months. Signals which were identified and given these priorities would take an unacceptable amount of time for further actions to be decided. One example was identified during the inspection:

[redacted] use was a signal identified as a result of PRR review of data from September 2018, on the 5th November 2018. The November 2018 signal triage meeting confirmed the signal was valid had assigned as "Category 2". The signal evaluation report was updated on the 26th of June 2019, with updates of the actions agreed during the signal evaluation meeting on the 24th June 2019, seven months after the

identification of the issue.

There were also signals which had been identified more than six months prior to the inspection, where a signal evaluation report was not yet available:

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The signal of [redacted] use causing amphetamine-positive urine drug screens was identified in September 2018 through a review of the PRR analysis. This signal was validated during the October 2018 signal triage meeting and assigned as a category 1 signal. No signal evaluation report had been produced at the time of the inspection and the signal had not been evaluated, 9 months after it had been initially detected.

Similarly, a signal of Atrial fibrillation had been identified with [redacted] use in October 2018, the signal had been validated during the December 2018 signal triage meeting and assigned as a category 1.

No signal evaluation report had been identified at the time of the inspection and the signal had not been evaluated, 9 months after it had been initially detected.

MHRA expectation is that the signal management process, from detection to evaluation and actions decided, has an upper boundary of six months. Teva's process does not ensure that signals which have been identified would have been evaluated and had further actions decided within this timeframe.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Deliverable(s)	Due Date(s)

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[redacted]

Preventative Action(s)
[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Finding MA.2 b)
As part of signal detection activities, Teva were performing disproportionality analysis on data from the global safety database, using a Proportional Reporting Ratio (PRR) calculation. This was being performed on a monthly basis for all products excluding [redacted] Teva had not set criteria for which types of cases should be included within the disproportionality analysis and confirmed that events identified from solicited sources were being included. The inclusion of solicited events within disproportionality can impact upon the sensitivity of the analysis, including producing false positives or masking potential signals.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]

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[redacted]

Corrective Action(s)

[redacted]

Preventative Action(s)

[redacted]

Finding MA.2 c)
Signal detection and evaluation activities did not incorporate the requirements outlined in GVP P.II regarding biological medicines. The signal detection activities being performed by Teva did not include any information regarding the batches associated with ADRs for biological medicines, resulting in Teva not being able to identify or detect differences between batches of the same product.

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There was no procedural requirement for signals which had been identified for biological medicines to be evaluated in the context of batch-specific data.

TEVA were in the process of aligning their change control procedures with the requirements outlined in GVP P.II. regarding making assessments for updating the RMP following the change of a manufacturing process. [redacted] Change control" [redacted] had been updated to include pharmacovigilance as one of the change evaluator functions upon a change of manufacturing process for biological medicines; this described that, if required, a cross-functional team would be set-up to discuss the impact of the changes.

There was a procedure in draft, shown to the inspection team which detailed the process from the time of a potential change, to the initiation of a change control (in line with [redacted] outlined above) and the set-up of a cross-functional team regarding changes to the manufacturing processes.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Preventative Action(s)

[redacted]

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[redacted]

Comment
Following the supervisory authority inspection, Teva had begun implementing a risk-based approach to signal detection, moving away from a monthly review for all products, to a scale of monthly, three-monthly and six-monthly review, depending on risk assignment. Teva had also committed to the supervisory authority as CAPA to conduct a retrospective signal detection activity covering a three-year period for all products. During this inspection, the link between a large number [redacted] of duplicate cases following the Allergan generics portfolio acquisition and their inclusion in disproportionality analysis was discussed with Teva. All disproportionality analysis conducted since the time of the Allergan portfolio data migrations would have been impacted by the inclusion of the [redacted] duplicates, and further impacted as these duplicates were investigated and managed until the completion of the activity in mid-2018. The impact of the duplicate data on the denominator data may have masked potential signals over the two-year period. The proposed retrospective signal detection activity covering the last three years will allow an opportunity to perform signal detection activities on the now "stable" denominator data. Teva should also consider the impact of finding MA.2 b) prior to performing this activity.

MA.3 Reference Safety Information

Requirements:

Directive 2001/83/EC as amended

Paragraph 40 "*The provisions governing the information supplied to users should provide a high degree of consumer protection, in order that medicinal products may be used correctly on the basis of full and comprehensible information.*"

Article 23(3) "*The marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge, including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004.*"

Official Journal of the European Union, 2013/C 223/01:

2.1.1. *"Minor variations of Type IA do not require prior examination by the authorities before they can be implemented by the holder."*

Q&A - List for the submission of variations according to Commission Regulation (EC) 1234/2008:

5.2. *"What is meant by "implementation" for Type IA variations?*
[…] For product information, it is when the Company internally approves the revised product information. The revised product information should normally be used in the next packaging run."

Product- or Population-Specific Considerations II: Biological medicinal products

P.II.B.1.1.4. *'As a general principle in order to improve traceability of biological medicines, all summaries of product characteristics (SmPCs) for biologicals (also with relevant appropriate wording in the package leaflets (PLs)) should include a prominent statement that the name and batch number of the administered product should be clearly recorded in the patient file. Related wording should also be included in relevant educational material, direct healthcare professional communication (see P.II.B.6.) and product promotional material as applicable.'*

Finding MA.3 a)

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There were deficiencies identified with the MAH updating external websites with updates to SmPCs and PILs.

a) The SmPCs for [redacted] and corresponding PILs published on company websites https://www.tevauk.com/hcp and https://www.tevauk.com/patients had not been updated following the submission of a type [redacted] variation to the MHRA on 08 May 2019; and did not include the uncommon ADR "dysphagia" in Section 4.8 of the SmPC and Section 4 of the PIL.

b) Delays were identified with uploading updated SmPCs and PILs to the electronic medicines compendium (EMC) website (https://www.medicines.org.uk/emc).

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i) A variation to add warnings regarding daytime sleepiness and sudden sleep onset episodes and to remove dysphoria as a symptom of overdose from the product information for [redacted] was approved on 01-Sep-2017. The SmPC was updated on the EMC on 24-Oct-2017, a delay of over a month, and the PIL was updated on the EMC on the 16-Nov-2017, a delay of over two months.

Inspector addition following the issuance of the inspection report. Further documentation was provided which supported the timeframes for upload of the SmPC to the EMC. A linguistic review was required by the EMA for this change and this was completed on the 16-Oct-2017. However, the PIL remained non-compliant as it was uploaded one month following the completion of the linguistic review.

ii) A variation to add a drug-drug interaction with [redacted] and a warning regarding hyperalgesia for Actiq was approved on 09-Oct-2018, both SmPC and PIL were updated to the EMC on the 06-Nov-2018, representing a delay of almost one month.

iii) A type [redacted] variation to add a warning of visual disturbances for [redacted] was submitted to the EMA on the 10-May-2017, the application form included an implementation date of the 10-May-2017. The EMC was not updated until the 14-June-2017, representing a delay of just over one month.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

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[redacted]

Corrective Action(s)	
[redacted]	
Deliverable(s)	**Due Date(s)**
[redacted]	
Preventative Action(s)	
[redacted]	
Deliverable(s)	**Due Date(s)**
[redacted]	

Finding MA.3 b)

There were deficiencies identified with the maintenance of reference safety information.

a) A delay of over two months was identified for the submission of a safety variation for [redacted] to include a warning on the risk of aortitis in line with PRAC recommendation on signals [redacted] published on 05-March-2018. The PRAC recommendation issued a deadline of two months, however variation [redacted] was submitted on the 17-Aug-2018.

b) The product information for [redacted] had not been updated to include the ADR 'Kounis syndrome' into Section 4.8 of the SmPC,

despite a letter from the MHRA on 23 March 2017 to implement this addition.

c) The Teva product portfolio included six biological medicines. The following deficiencies were seen in relation to the inclusion of wording on the traceability of biological medicines as required by GVP PII:

i) The SmPC and PIL of the following products did not include a prominent statement that the name and batch number of the administered product should be clearly recorded in the patient file:

- [redacted] dated 03 September 2018
- [redacted] dated 15 June 2018
- [redacted] dated 21 March 2019.
- [redacted] dated 18 September 2018

ii) The PIL of [redacted] dated March 2019, did not include a prominent statement that the name and batch number of the administered product should be clearly recorded in the patient file.

iii) While the SmPCs for [redacted] dated 04 May 2018) contained the following statement in section 4.4 Special warnings and precautions for use 'In order to improve the traceability of epoetins, the name of the administered epoetin should be clearly recorded in the patient file.', no reference was made to the need to record the batch number of the administered product. In addition, no statement on the traceability was included in the respective PILs.

iv) The PIL (dated April 2019) and HCP [redacted], dated November 2015) for [redacted] did not include a prominent statement that the name and batch number of the administered product should be clearly recorded in the patient file.

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[redacted]

Root Cause Analysis

[redacted]

Section 43

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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Deliverable(s)	Due Date(s)
[redacted]	

Preventative Action(s)
[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

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Finding MA.3 c)
Teva had failed to implement an updated PIL for [redacted]-release tablet [redacted] into packs within 6 months following the approval of a safety variation. There was one batch [redacted] expiry date November 2020, none remaining in stock) containing the out-of-date PIL [redacted] dated March 2016) which was QP released on 26-July-2018, almost eight months after variation approval. As part of the variation, PIL section 4 "Possible side effects" was aligned with SPC section 4.8 to include the ADRs of 'decreased haemoglobin' and 'increased eosinophils' and to re-arrange the order of ADRs in line with the QRD template to list serious ADRs first. MHRA published guidance (https://www.gov.uk/guidance/medicines-packaging-labelling-and-patient-information-leaflets) states that changes to labels, leaflets and packaging must be introduced within 3 to 6 months of variation approval so that it is ensured that the outdated labelling is not released to the market beyond this time
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]
Preventative Action(s)
[redacted]

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[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

MA.4 Management and Reporting of Adverse Drug Reactions

Requirements:

Directive 2001/83/EC as amended

Article 107 (4) *"Marketing authorisation holders shall establish procedures in order to obtain accurate and verifiable data for the scientific evaluation of suspected adverse reaction reports. They shall also collect follow-up information on these reports and submit the updates to the Eudravigilance database.*

Commission Implementing Regulation 520/2012

Article 11 (1) *"Specific quality system procedures and processes shall be in place in order to ensure the following:*
[…] c) the submission of accurate and verifiable data on serious and non-serious adverse reactions to the Eudravigilance database within the time limits provided for in the first and second subparagraphs respectively of Article 107(3) of Directive 2001/83/EC"

GVP Module VI - Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)

VI.B.5 *"Conformity of stored data with initial and follow-up reports should be verified by quality control procedures, which permit for the validation against the original data or images thereof. With regard to this, the source data (e.g. letters, emails, records of telephone calls, which include details of an event) or an image of the source data should be easily accessible."*

Finding MA.4 a)

There were deficiencies identified with the processes in place to ensure accuracy and conformity between source documentation and the cases stored within the global safety database.

Teva affiliates were using the Data Exchange and Local Tracking of Adverse (DELTA) system, to initially code cases prior to sending them for full case processing into ARISg. However, source documents were not transferred with the cases when they were transmitted from DELTA to ARISg for further processing, and all information which was not coded into specific fields was to be manually included into the narrative in accordance with [redacted] "Manual for the Data Exchange and Local Tracking of Adverse events (DELTA) system" ([redacted] effective 30 Nov 2017).

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The following deficiencies were identified:

a) Personnel processing cases into ARISg did not have the opportunity to confirm the details being entered against source documents.

b) There was a failure to adhere to the local procedure for the QC of cases in the Data Exchange and Local Tracking of Adverse events (DELTA) system.

According to UK/IE Local Addendum to Global PhV [redacted] "UK/IE [redacted] (edition status 03, effective 18 Oct 2018) 'Handling and

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Reporting Adverse Events/Adverse Drug Reactions and Special Situations for Teva's Products' (superseded by [redacted] effective 18 July 2019 with no change to quoted section), all serious, potential litigation, clinical trial/study and literature cases in DELTA undergo QC against source documents by the LSOs, before transfer to ARISg. In addition, a weekly QC is conducted on a [redacted] random selection of all cases in DELTA.

The addendum states: "If the error rating is above [redacted] a larger sample size and/or extended period of time will need to be evaluated and sampled".

The check of [redacted] received during week commencing 10th December 2018 found that [redacted] contained errors, 'AE added (mentioned in narrative)' and 'Changes to AE term (verbatim)'. The MAH confirmed that these cases were corrected, and verbal feedback was provided to relevant personnel however no further action had been taken with regards to expanding the sample size.

c) The following errors were identified in the 15 cases from ARISg that were reviewed by inspectors:

i) Spontaneous UK case [redacted] received from a consumer on 09-Jan-2018 of 'maternal exposure during pregnancy' with [redacted] stated "Mother was breastfeeding". There was no indication in the source documentation of breastfeeding, and it was confirmed by the MAH that this error resulted from a technical error in the mapping of data from Delta to the automated case narrative.

Teva stated that a ticket had been raised with ARISg concerning this issue (defect [redacted] detected date 13 December 2013) and case processors were notified of the issue, however no retrospective correction had been performed on the affected cases.

This case was submitted to EudraVigilance on 22-Feb-2018 with the incorrect information in the case narrative.

ii) Spontaneous UK case [redacted] received from a consumer on 09-May-2018 regarding a patient who experienced multiple adverse events after receiving [redacted] was hospitalised and subsequently died. The autopsy report was provided as follow-up information to the case on 11-Sept-2018. The case incorrectly included the term 'sudden death' coded as an event from the verbatim "admitted to hospital and died" (in addition to PTs: 'pneumonia aspiration, 'mouth ulceration', 'mastication disorder', 'dysphagia' and 'oral candidiasis'). The autopsy report stated the cause of death was 'aspiration bronchopneumonia', however the event term of 'sudden death' remained in the case.

[redacted]

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

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[redacted]

Corrective Action(s)
[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Preventative Action(s)
[redacted]

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[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Finding MA.4 b)

Other case processing deficiencies included:

a) One case [redacted] was identified where follow-up had not been conducted as per company procedures. [redacted] "Follow-up for medicinal products-Questions and Answers", [redacted] outlined that a minimum of two requests of follow-up should be made for serious cases.

b) There were a small number of post-marketing solicited cases which had been allocated an incorrect case type:

i) Case number [redacted] (all versions of the case) reported under protocol [redacted] was recorded as a clinical trial case.

ii) Case number [redacted] 3 versions of the case) reported under protocol [redacted] was recorded as a clinical trial case.

iii) Case numbers [redacted] of the case), [redacted] version of the case), [redacted] version of the case), [redacted] versions of the case), [redacted] reported under protocol [redacted] were recorded as clinical trial or compassionate use cases.

Root Cause Analysis

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[redacted]

Further Assessment

[redacted]

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[redacted]

Corrective Action(s)

[redacted]

[redacted]

Preventative Action(s)

[redacted]

[redacted]

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[redacted]

[redacted]

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

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Corrective Action(s)	
[redacted]	
[redacted]	[redacted]
Preventative Action(s)	
[redacted]	
Deliverable(s)	**Due Date(s)**
[redacted]	

MA.5 Pharmacovigilance System Master File

Requirements:

GVP Module II – Pharmacovigilance System Master File

II.B.4.7. "*The PSMF shall also contain a note associated with any audit where significant findings are raised. […]The note and associated corrective and preventative action(s), shall be documented in the PSMF until the corrective and/or preventative action(s) have been fully implemented, that is, the note is only removed once corrective action and/or sufficient improvement can be demonstrated or has been independently verified.*

The master file shall also document deviations from pharmacovigilance procedures, their impact and management until resolved [IR Art 4(3)]. This may be documented in the form of a list referencing a deviation report, and its date and procedure concerned."

II.B.4.8. "*An annex to the PSMF shall contain the following documents:*

- *A list of medicinal products covered by the PSMF including the name of the medicinal product, the international non-proprietary name of the active substance(s), and the Member State(s) in which the authorisation is valid*

  The list of medicinal products authorised in the EU should also include the authorisation number(s) including, per authorisation:

  […] - the presence on the market in the EU

  […] The list should be organised per active substance and, where applicable, should indicate what type of product specific safety monitoring requirements exist (for example risk minimisation measures contained in the risk management plan or laid down as conditions of the marketing authorisation, non-standard PSUR periodicity, referral under Article 31 of Directive 2001/83/EC, or included in the list described in Article 23 of Regulation (EC) No 726/2004). The monitoring information may be provided as a secondary list."

Human Medicines Regulations 2012 Regulation 73 (1-5)

Finding MA.5 a)

The following identified non-compliances were not included in the PSMF (dated 26 June 2019):

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a) A defect in ARISg that had been identified to be affecting multiple cases and was being resolved was not presented in the PSMF as a deviation from pharmacovigilance processes (as reported in finding MA.4 a). Ticket [redacted] regarding the 'narrative from Delta is not completely transferred into Arisg' was raised in the ArisGlobal support system in December 2018 and was ongoing at the time of the inspection. A work around was in place to ensure that case processors checked summary sheets attached to cases to ensure data in cases was accurate and complete.

b) The non-compliances identified at the audit of Bupa Home Healthcare Limited/Lloyds Pharmacy Clinical Homecare (GB) were not presented in the PSMF.

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Annex G 'List of Scheduled and Completed PhV Audits' [redacted], dated 26-June-2019) stated that this audit was conducted on 04-Oct-2018 and was completed. However, it was confirmed during the inspection that, although the onsite audit was conducted on 04-Oct-2018, the draft audit report (issued to the auditee on 18-June-2019), remained un-finalised. As a result, the significant findings associated with this audit (1 critical and 3 major findings in the draft report) were not presented in the PSMF, and there was no note in the PSMF to show that there were unresolved findings associated with this audit.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

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[redacted]

Corrective Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Preventative Action(s)

[redacted]

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[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Finding MA.5 b)

The following deficiencies were identified as to the product portfolio outlined in the PSMF [redacted]

a) There were discrepancies in the information on the marketing status of products held by MHRA and provided in the PSMF. There were two examples of products that were listed as "not marketed" in PSMF Annex H (part of PSMF dated 26 June 2019) but were listed as 'marketed' in the MHRA system:

i) [redacted]

b) Annex H incorrectly included [redacted] concentrate and solvent for solution for infusion ([redacted] The UK MA was cancelled on 30 May 2019.

c) Annex H3 "RMP tracker [redacted] incorrectly included two UK-authorised products which had RMP commitments:

i) [redacted] was listed as a UK authorised product with a DHPC and an education programme for patients listed. However, Teva confirmed the product licence [redacted] had been cancelled on 04 July 2018.

ii) [redacted] was listed as a UK authorised product with a patient alert card associated with it. However, Teva confirmed that the product licences (PL [redacted] had been cancelled on 29 June 2018.

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Preventative Action(s)

[redacted]

Deliverable(s)	Due Date(s)

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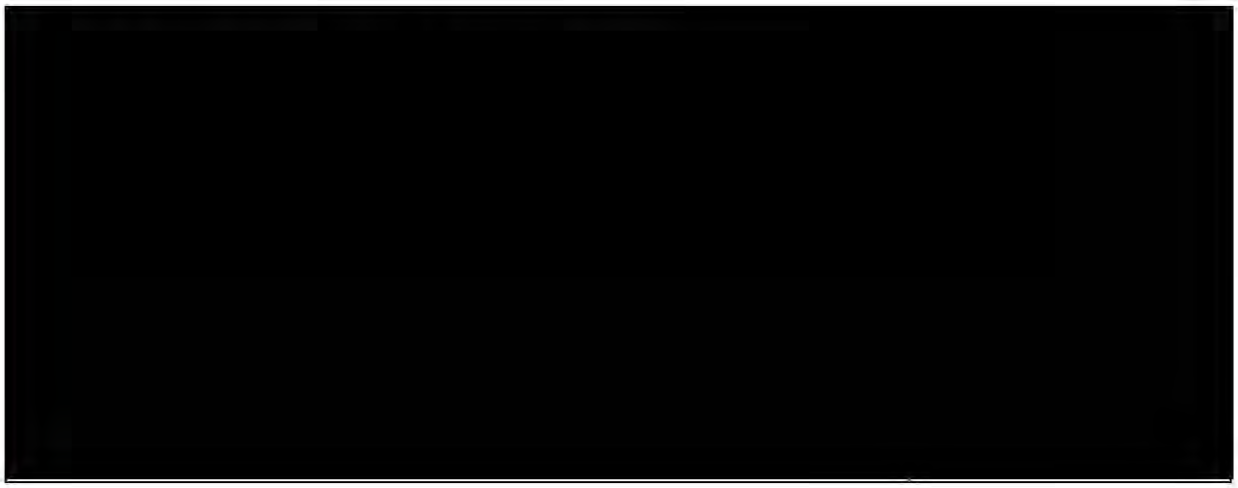

C.4.3 Minor findings

MI.1 Pharmacovigilance Audits

Finding MI.1 a)
Delays were identified in finalising CAPA plans from audit, with one example with significant findings that did not have CAPA plans agreed at the time of the inspection, 10 months after the audit was completed. Specifically: a) The audit of Patient Services and Solutions, Inc. (Teva), USA was conducted on 26 Sept 2018. This is the internal Teva group that manages all US Patient Support Programs. This audit outcome included 3 major findings (recorded in module 7 of PSMF v28, dated 26 June 2019): • *Computer systems processes are missing or not adequately documented* • *Although a new vendor (AssistRx) is actively providing services to Teva for all Teva sponsored patient support programs, there is no final, signed, and executed Master Service Agreement (MSA) or Statement of Work (SOW) in place. As of April 2019, Patient Services and Solutions Inc. activities are performed by the vendor, Assist Rx.* • *There are deficiencies in adverse event training and documentation for PSS staff and vendors* Evidence was reviewed which demonstrated Teva had been requesting a response to the comments provided on the draft CAPA plan. However, there had been no finalised CAPA plan agreed 10 months after the audit.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]

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	(completed)
Preventative Action(s)	
[redacted]	
Deliverable(s)	**Due Date(s)**
[redacted]	

MI.2 Periodic Safety Update Reports

Finding MI.2 a)
Teva confirmed that they were not excluding non-related spontaneous reports within the cumulative summary tabulations in PSURs. This has been graded as a minor finding as the impact could not be determined during the inspection. [redacted]
Root Cause Analysis
[redacted]
Further Assessment
[redacted]

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[redacted]

Corrective Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Preventative Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

MI.3 Risk Management

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Finding MI.3 a)
The RMP for [redacted] includes a category 3 "required" study to assess the incidence and clinical implications of anti-G-CSF antibodies. The RMP states that this will be monitored through the use of data provided by the [redacted] The contract between Teva and the [redacted] was reviewed during the inspection and had ended on the 31 Jan 2019, five months prior to the inspection. Teva confirmed they had been receiving data as normal, including a report in March 2019 so the impact was nominal. Teva also contacted the [redacted] during the inspection to confirm that the agreement would be prolonged past the 31-Jan-2019 without any gap in documentation, this e-mail exchange was reviewed by the inspection team.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]
Preventative Action(s)
[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

SECTION D: CONCLUSIONS AND RECOMMENDATIONS

D.1 Conclusions

The factual matter contained in the Inspection Report relates only to those things that the inspection team saw and heard during the inspection process. The Inspection Report is not to be taken as implying a satisfactory state of affairs in documentation, premises, equipment, personnel or procedures not examined during the inspection. It is recommended that you review whether the inspection findings also apply to areas not examined during the inspection and take appropriate action, as necessary.

The responses to the inspection findings, which include proposed corrective and preventative actions, do appear to adequately address the issues identified. When the company has adequately implemented the proposed corrective and preventative actions, the pharmacovigilance system will be considered to be in general compliance with applicable legislation.

Teva are required to provide updates to the Lead Inspector with regards to MA.1 on a quarterly basis. This commitment has been agreed to as outlined in appendix III, and should begin upon receipt of information from Allergan.

D.2 Recommendations

The Lead Inspector has recommended that the next MHRA inspection is performed as part of the routine risk-based national inspection programme.

APPENDIX I REFERENCE TEXTS

- Regulation (EC) No. 726/2004 (Title II, Chapter 3), as amended.
- Directive 2001/83/EC, as amended.
- Commission Implementing Regulation (EU) No 520/2012.
- Commission Implementing Regulation (EU) No 198/2013.
- Guideline on good pharmacovigilance practices (GVP).
- Directives 2001/20/EC and 2005/28/EC in relation to Clinical Trials.
- The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916).
- CPMP/ICH/377/95: E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting".
- EMA/CHMP/ICH/287/1995: ICH guideline E2B (R3) on electronic transmission of individual case safety reports (ICSRs) - data elements and message specification - implementation guide.
- EMA/CHMP/ICH/544553/1998: ICH guideline E2C (R2) on periodic benefit-risk evaluation report (PBRER).
- CPMP/ICH/3945/03: E2D "Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting".
- CPMP/ICH/5716/03: E2E "Pharmacovigilance Planning".
- CHMP/ICH/309348/2008: E2F "Development safety update reports".
- EMA/CHMP/ICH/135/1995: E6 (R2) "Guideline for good clinical practice".
- Eudralex Volume 10, Chapter II: Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT3'), June 2011.
- EMEA/CHMP/313666/2005: "Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data".
- EMEA/CHMP/PhVWP/235910/2005: "Guideline on conduct of pharmacovigilance for medicines used by the paediatric population".

APPENDIX II MA.1 A) MIGRATED CASE DETAILS

The tables below show the oldest and most recent cases which had been migrated from the legacy company databases to Teva.

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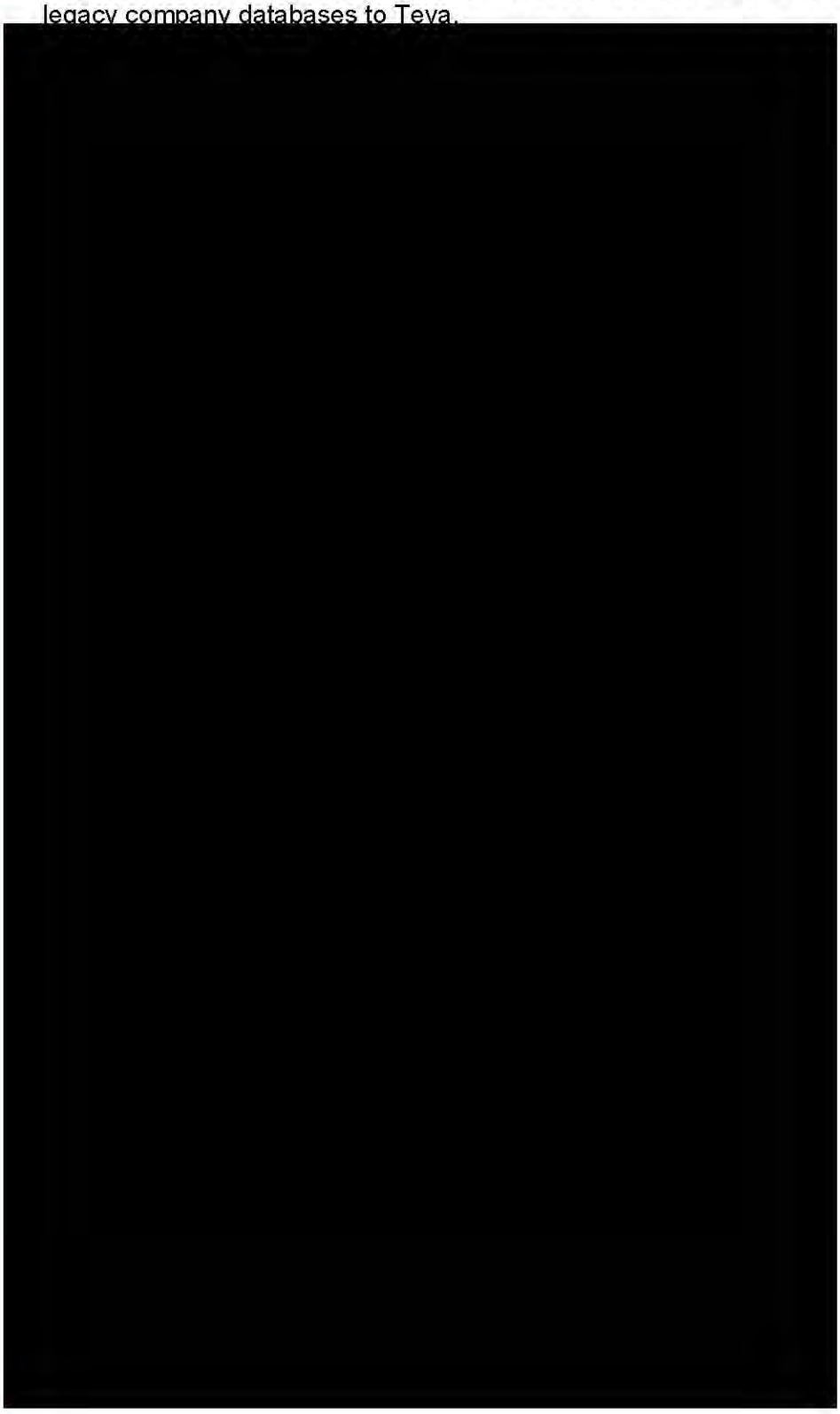

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APPENDIX IV PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	TBC	**DAY**	1
PHARMACOVIGILANCE INSPECTION OF	TEVA	**DATE**	Tuesday 23rd July 2019
LOCATION	Field House, Station Approach, Harlow CM20 2FB	**START TIME**	09:30 arrival for 10:00 opening meeting

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Opening Meeting Review of scope of inspection and inspection plan **Company Presentation** Overview of the company, the pharmacovigilance system and the quality system. Include details of acquisitions / divestitures in the last 3 years. *(approx. 20 minutes)*		[redacted]
Case Processing, including but not limited to: - Data entry, - MedDRA coding - Case assessments	[redacted]	

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- Expedited reporting - Follow-up processes Please provide access to the live database (ArisG) during this session.		[redacted]
LUNCH	-	-

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Risk Management, including but not limited to: - Additional risk minimization in the UK - Registries	[redacted]	[redacted]

MHRA INSPECTION NUMBER	TBC	**DAY**	2
PHARMACOVIGILANCE INSPECTION OF	TEVA	**DATE**	Wednesday 24th July 2019
LOCATION	Field House, Station Approach, Harlow CM20 2FB	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Reference Safety Information, including but not limited to: - Maintenance of CCSI and local labelling - Post-approval pathways	[redacted]	[redacted]
LUNCH	-	-

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Signal Management, including but not limited to: - Qualitative methodologies used for signal detection - Quantitative methodologies used for signal detection - Signal assessment / evaluation - Quality systems supporting signal management activities	[redacted]	[redacted]

Section 40

Solicited sources of safety data, including but not limited to: - Market research programmes - Patient support programmes - Non-interventional studies	[redacted]	[redacted]

MHRA INSPECTION NUMBER	TBC	**DAY**	3
PHARMACOVIGILANCE INSPECTION OF	TEVA	**DATE**	Thursday 25th July 2019
LOCATION	Field House, Station Approach, Harlow CM20 2FB	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Pharmacovigilance data management, including but not limited to: - Data migrations - Retrieval of data from the DB (including PSUR searches)	[redacted]	[redacted]

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LUNCH	-	-
Quality Management System, including but not limited to: - Deviation and CAPA management	[redacted]	[redacted]
Document Review	-	Inspectors only

MHRA INSPECTION NUMBER	TBC	**DAY**	4
PHARMACOVIGILANCE INSPECTION OF	TEVA	**DATE**	Friday 26th July 2019
LOCATION	Field House, Station Approach, Harlow CM20 2FB	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
This day is kept free for ad-hoc meetings and document review		Interviewee(s) as required.
Inspectors meeting	-	Inspectors only
Closing meeting	-	All welcome